II. Remarks

A. Status of the claims

Claims 1-2 and 5-19 are currently pending. No amendments to the claims have been made herein.

B. Rejections under 35 U.S.C. § 103

1. U.S. Patent No. 5,149,538 to Granger et al. in view of U.S. Patent No. 5,891,919 to Blum et al.

Claims 1, 2 and 5-18 were rejected under 35 U.S.C. §103(a) over U.S. Patent No. 5,149,538 to Granger et al. ("the Granger patent") in view of U.S. Patent No. 5,891,919 to Blum et al. ("the Blum patent"). The Examiner acknowledged that the Granger patent "does not teach the use of an emetic, nauseant, flavoring substance, ergolide, bitter quaternary ammonium compound, or atropine as a distressing agent in a transdermal formulation of an opioid analgesic." See Office Action, page 3. However, the Examiner asserted that one skilled in the art "would know that the agent described by Blum et al. would be a suitable substitude" for an opioid antagonist described in the Granger patent. See Office Action, page 4.

Applicant respectfully disagrees.

The Granger patent describes a transdermal dosage form that comprises an opioid permeable to the skin and, separately, an opioid antagonist which is releasable from the dosage form upon being ingested or substantially immersed in a solvent. See, e.g., Abstract. The purpose of the opioid antagonist described in the Granger patent is, e.g., to reduce misuse or abuse of the opioid **by attenuating the euphorigenic effect of the opioid**. See, e.g., column 2, lines 62-64 ("... the antagonist substance substantially

attenuates the euphorigenic effect of the opioid, thereby reducing the tendency for misuse and abuse of the dosage form").

The Blum patent describes the use of denatonium capsaicinate as a substance providing a bitter and/or spicy flavour for use "as an aversive agent, biocide, antifoulant and flavorant ...". See Abstract. However, the Blum patent fails to teach or suggest that denatonium capsaicinate and other compounds described in therein would attenuate the euphorigenic effect of an opioid.

As stated above, attenuating the euphorigenic effect of the opioid is the purpose of the opioid antagonist in the Granger patent.

Accordingly, Applicant submits that, contrary to the Examiner's assertion, one skilled in the art would not have considered that compounds described in the Blum patent (e.g., denatonium capsaicinate) would be substitutable for the opioid antagonist in the Blum reference, as the Blum patent fails to provide any indication that compounds described therein would attenuate the euphorigenic effect of an opioid (which is the purpose of the opioid antagonist in the Granger patent).

In fact, Applicant submits that replacing the opioid antagonist in the Granger patent with denatonium capsaicinate of the Blum patent would render the Granger patent unsuitable for its intended purpose (i.e., to attenuate the euphorigenic effect of the opioid by use of an opioid antagonist). Accordingly, Applicant submits that there is no suggestion to make the Examiner's proposed modification. See, e.g., MPEP, Section 2143.01 ("[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification ...").

Applicant also submits that the Blum patent further fails to teach or suggest that denatonium capsaicinate is suitable for inclusion within a transdermal system for

delivering opioid analgesics to humans, let alone the transdermal system of the Granger patent.

With regard to the Examiner's statement that denatonium capsaicinate of the Blum patent "may be incorporated into topical formulations and dressings ... (see column 4, lines 38 to 43), Applicant notes that the Blum patent states that this is done "*in order to prevent animals from removing these materials by biting, gnawing, chewing or licking after veterinarial procedures.*" [emphasis added]. Accordingly, Applicant submits that the addition of denatonium capsaicinate to medical dressings and topical formulations described in the Blum patent is purely in the context of veterinary medicine where its aim is, e.g., to prevent animals interfering with wound healing after treatment.

Applicant respectfully reiterates that there is no teaching or suggestion in the Blum patent that denatonium capsaicinate is capable of attenuating the euphorigenic effect of an opioid, which is required of the opioid antagonist in the Granger patent.

Accordingly, Applicant submits that the combination of the Granger patent and the Blum patent would not have suggested to one skilled in art to substitute an opioid antagonist in the transdermal system of the Granger patent with denatonium capsaicinate of the Blum patent. In fact, Applicant submits that the proposed modification would render the Granger patent unsuitable for its intended purpose, at least for the reasons set forth above.

Applicant further submits that the Granger patent does not teach or suggest "distressing" the user as recited in the present claims. Instead, it describes "attenuating" the euphorigenic effect of the opioid of the described dosage form by use of an opioid antagonist. Therefore, Applicants submit that when considered as a whole, the Granger patent teaches merely to attenuate the euphorigenic effect of an opioid by use of an antagonist substance, rather than to distress the user as recited in the present claims.

The Blum patent, on the other hand, teaches the use of denatonium capsaicinate as a substance providing a bitter and/or spicy flavour for use as an aversive agent. Applicant submits that, while denatonium capsaicinate may be an aversive agent, it is not an opioid antagonist capable of attenuating the euphorigenic effect of an opioid (which is required of the opioid antagonist in the Granger patent).

Therefore, Applicant submits that the combination of the Granger patent and the Blum patent would not have logically provided a reason for one skilled in the art to replace the opioid antagonist of the Granger patent which necessarily attenuates the euphorigenic effect of the opioid when used as intended with denatonium capsaicinate which is **unable** to attenuate the euphorigenic effect of the opioid.

Furthermore, as indicated previously, the Blum patent offers no incentive to the skilled person to use denatonium capsaicinate as a distressing substance in a transdermal system for delivering opioids to humans, let alone the transdermal system described in the Granger patent.

For the foregoing reasons, Applicant submits that the combination of the Granger patent and the Blum patent would not have suggested to one skilled in the art the compositions of the present claims.

Accordingly, withdrawal of the rejection is respectfully requested.

2. U.S. Patent No. 5,149,538 to Granger et al. in view of U.S. Patent No. 4,175,119

Claims 1, 2 and 5-19 were rejected under 35 U.S.C. § 103(a) over the Granger patent in view of U.S. Patent No. 4,175,119 to Porter et al. ("the Porter patent"). The Examiner acknowledged that the Granger patent "does not teach the use of an emetic, nauseant, flavoring substance, ergolide, bitter quaternary ammonium compound, or atropine as a distressing agent in a transdermal formulation of an opioid analgesic." See

Office Action, page 5. However, the Examiner asserted that "one skilled in the art would know that the emetic described by Porter would be a suitable substitute" for the opioid antagonist of the Granger patent. See Office Action, page 5 and 6.

Applicant respectfully disagrees.

Applicant submits that the Porter patent describes a method of preventing overdosage of a therapeutic composition, e.g., a tablet or capsule, by coating the surface of the therapeutic composition with a certain amount of an emetic chemical. The idea is, e.g., that if the correct dosage is taken then no emetic effect will be produced whereas if an overdose is taken emesis will ensue; and/or that, in the event of an overdose, the emetic is the first active ingredient to be dissolved or touch the gastric lining so as to induce emesis. The Porter patent specifically states that "[i]s important in this invention that the therapeutic composition be enveloped or coated with the emetic chemical instead of commingling or admixing the emetic chemical with the therapeutic composition." See Column 2, lines 59-62.

Applicant submits that this teaching is **incompatible** with the transdermal device described in the Granger patent. Applicant notes that the opioid antagonist in the Granger patent is not enveloped or coated on the composition, but is instead commingled or admixed in the composition. See e.g., the Granger patent, Figures 1-4; see also column 6, line 20 to column 7, line 31. In fact, Applicant submits that the misuse of transdermal system of the Granger patent would necessarily result in admixing of the opioid and emetic chemical.

Accordingly, Applicant submits that the combined teachings of the Granger patent and the Porter patent would not have suggested to one skilled in the art to replace the opioid antagonist in the Granger patent with the emetics of the Porter patent in transdermal devices of the Granger patent, at the very least because the proposed

modification is contrary to the teachings of the Porter patent and is incompatible with the transdermal device of the Granger patent.

Further, as stated above, the purpose of the opioid antagonist described in the Granger patent is, e.g., to reduce misuse or abuse of the opioid **by attenuating the euphorigenic effect of the opioid**. See, e.g., column 2, lines 62-64 ("... the antagonist substance substantially attenuates the euphorigenic effect of the opioid, thereby reducing the tendency for misuse and abuse of the dosage form").

Applicant submits that there is no disclosure in the Porter patent that emetics described therein are capable of attenuating the euphorigenic effect of an opioid. In fact, Applicant submits that none of the emetic chemicals mentioned in the Porter patent are opioid antagonists.

Accordingly, Applicant submits that the combination of the Granger patent and the Porter patent would not have suggested to one skilled in the art to replace the opioid antagonist (a substance which attenuates the euphorigenic effect of an opioid) with an emetic (a substance is **unable** to attenuate the euphorigenic effect of the opioid). See, e.g., MPEP, Section 2143.01 (... "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification ...").

Applicant further submits that the Porter patent does not teach or suggest that the emetics mentioned therein are suitable for use as a distressing substance within a transdermal system for delivering opioids, let alone a transdermal delivery system of the Granger patent.

For the foregoing reasons, Applicant submits that the combination of the Granger patent and the Porter patent does not render the present claims obvious, and respectfully request withdrawal of the rejection.

III. CONCLUSION

An early and favorable action is earnestly solicited. In view of currently recommended Patent Office policy, the Examiner is invited to contact the undersigned in the event that a telephonic interview would advance the prosecution of this application.

Respectfully submitted,
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